Environmental Health Perspectives Supplements
101 (Suppl. 2): 159–167 (1993)

Impact of the Environment on Reproductive Health: Executive Summary

by Frank Michal,[1] Kenneth M. Grigor,[2] Andrés Negro-Vilar,[3] and Niels E. Skakkebæk[4]

The papers presented at the workshop on the "Impact of the Environment on Reproductive Health" are published in this issue of the *EHP Supplements*. After the formal presentation of the papers, the authors and scientists met to discuss the important aspects of environmental issues affecting human reproductive health. This Executive Summary was compiled by the organizers and editors of the workshop and the proceedings.

Introduction

The late 1980s witnessed the elevation of environmental issues to the highest levels of governments. Concern has been focused on global issues such as climatic change, stratospheric ozone depletion, long range transport of air pollution, export of toxic wastes, acid deposition, and loss of biological diversity. These concerns remind us of the vital interdependence of human beings and nature and have sensitized political consciousness at national, local and individual levels.

The international workshop convened by the World Health Organization Special Programme of Research, Development and Research Training in Human Reproduction on September 30–October 4, 1991, congregating scientists from all parts of the world focused attention on the impact of the environment on human reproductive health. The workshop was held in the World Health Organization (WHO) European Regional Office, Copenhagen, in collaboration with the Danish Ministry of the Environment, the Danish Ministry of Health, the Danish Medical Research Council, the Commission of the European Communities, the International Programme on Chemical Safety and the U.S. National Institute of Environmental Health Sciences. The local organization was undertaken by the University Department of Growth and Reproduction, Rigshospitalet, Copenhagen.

Definitions

The ability of an organism to reproduce is essential for its survival and the reproductive process is particularly vulnerable to adverse environmental conditions. Reproductive health is defined as a condition in which the reproductive process is accomplished in a state of complete physical, mental and social well being; it is not merely the absence of disease or disorders of the reproductive process. Reproductive health encompasses a wide area of health and environmental issues and concerns. One paradox is that while experiencing a population explosion, especially in developing countries, some of the same people suffer from infertility which can often be traced to environmental causes.

Environment represents all physical, biological, cultural, behavioral and socioeconomic factors or conditions surrounding the human organism. The interaction between humans and their environment is a continuous and complex process leading to man's adaptation to different environmental conditions around the world. This interaction often has been beneficial but in other situations produces adverse effects on human reproductive health.

In some regions of the world, problems associated with reproduction are largely attributable to socioeconomic and cultural influences. In other parts of the world, pollution is the major environmental factor. Pollution comes from industrial and natural sources and chemicals are entering the environment in ever-increasing quantities. It is difficult to assess the effect of human exposure to particular substances because multiple chemicals are frequently involved and these are superimposed on cultural and socioeconomic factors.

[1]Special Programme of Research, Development and Research Training in Human Reproduction, World Health Organization, Geneva, Switzerland.
[2]Department of Pathology, Edinburgh University, Edinburgh, UK.
[3]Laboratory of Molecular and Integrative Neuroscience, National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709.
[4]University Department of Growth and Reproduction, Rigshospitalet, Copenhagen, Denmark.
This manuscript was presented at the Conference on the Impact of the Environment on Reproductive Health that was held 30 September–4 October 1991 in Copenhagen, Denmark.

Chemical pollutants are considered to be the greatest threat to reproductive health in developed countries. However, as a global problem, the major factors in descending order of importance are infection, malnutrition, chemicals, radiation, and stress. In less developed countries, the added effects of socioeconomic and cultural influences become more evident.

Environmental Factors Affecting Reproductive Health

Chemicals

Chemical substances such as pharmaceuticals, agricultural and industrial chemicals, and household products are being continually introduced into the environment. These expose large population groups to polluted air, water, and soil in the workplace and at home. Environmental chemical contaminants are predominantly of local significance but can be carried over national borders for considerable distances.

Environmental chemicals are hazardous to human reproduction and development. Lead, methyl mercury, polychlorinated biphenyls (PCBs), alcohol and certain pharmaceuticals (e.g., retinoids, valproic acid, cytostatic drugs) are proven human developmental toxicants, and organic solvents, cadmium, carbon monoxide and anesthetic gases may have similar effects. Dibromochloropropane (DBCP), some glycol ethers, and lead are known to impair male fertility. Some natural and man-made environmental chemicals such as chlorinated hydrocarbons similarly affect the female sex hormone, estrogen. Prenatal and antenatal exposure may permanently damage the function of reproductlve organs.

Smoking during pregnancy has a marked deleterious effect on the developing brain and can result in permanent deficits in the child. Smoking also affects fetal growth and there is a well-established association between smoking by the mother and the incidence of respiratory disease in young children.

A number of agents affect reproduction in experimental animals, but the toxic effects on human reproduction of the vast majority of industrial and environmental chemicals are unknown.

Radiation

The part of the reproductive process most vulnerable to radiation injury is the testis where direct damage to the germinal epithelium will readily suppress development of the germ cells. The pregnant woman is also susceptible, and there is a rise in the incidence of miscarriages and stillbirths following radiation exposure. Animal studies indicate that exposure to radiation induces mutations in the genetic material of germ cells. Individuals at increased risk include workers in nuclear power stations and radioactive waste disposal units or those living in the vicinity of accidental release of radioactive compounds from such sites. There is also a risk to patients exposed to accidental "therapeutic overdose" or repeated diagnostic radiological investigations, and medical and paramedical personnel chronically exposed to diagnostic and therapeutic radiology.

In the event of accidental radiation leaks, it will be critical to calculate the degree of the radiation exposure and to compile an up-to-date register of the exposed population by accurate surveillance. Semen analysis and documentation of pregnancy outcomes will enable an accurate assessment of the magnitude and degree of the adverse reproductive effects.

Infections

Infections pose a major problem for reproductive health, particularly in the developing world. This has been exacerbated by the recent epidemic of HIV infection which, in some countries, has had a major impact on maternal and child mortality. In addition, it has resulted in an increase in the incidence of some infections such as tuberculosis. Infections can influence maternal health and fertility and also adversely affect the fetus and newborn infant.

Agents that infect the fetus directly include rubella, toxoplasma, syphilis, cytomegalovirus, and HIV. Other infections which may have an indirect influence on pregnancy outcome, through placental invasion, chorioamnionitis, or premature delivery, can result in fetal loss, prematurity, and increased prenatal mortality. Examples of such infections include malaria, tuberculosis, chlamydiosis, and listeriosis.

Infections such as those caused by herpes simplex virus, streptococcus, listeria, gonococcus, and tetanus may be acquired during delivery and result in acute severe infection in the newborn. Premature infants are particularly vulnerable to postnatal infections. Infants who acquire hepatitis B infection from their mothers at the time of birth are more likely to become chronic carriers with the risk of subsequent permanent liver damage and hepatocellular carcinoma, and contribute to the continuing high rate of hepatitis B infection within the population.

Rubella, cytomegalovirus, and toxoplasma can cause fetal damage which may not be apparent at birth and may not be manifest until later in childhood. Indeed, these infections are often asymptomatic during pregnancy and in the newborn, and a diagnosis of congenital infection is rarely made except in the severely affected children with classic manifestations.

Congenital syphilis poses a particular problem as it is potentially preventable. It has become uncommon in developed countries, but the reported increase in the United States is of concern. To prevent infections, it is important to improve general conditions and hygiene. In addition, disease patterns need to be monitored in communities and vaccination should be encouraged.

Malnutrition

Malnutrition involves not only a reduced intake of high-quality protein and energy-providing foods but also an inappropriate intake of essential vitamins and minerals: it affects both the pregnant woman and the growing child. In some countries with adequate food supplies, new methods of food production, manufacture, storage and supply have led to new hazards for pregnant women, such as the risk of infections from Salmonella and Listeria.

Stress

Neuroendocrine factors play an important role in reproduction. Reproductive health is likely to be affected by any interference with neuroendocrine homeostasis. Psychological, socioeconomic, and occupational stress from different environmental sources has been shown to exert a deleterious effect on the endocrine system governing various phases of the reproductive cycle. Consequently, improved environmental conditions and reduction of exposure to distressful stimuli and situations may lead directly to better reproductive health.

With increasing industrialization and a high proportion of both partners in the workforce, there is a growing threat to the family unit from such factors as shift work or night work in addition to other stresses in the workplace. This can affect the integrity of the sexual relationship and the family unit with consequences for healthy reproduction and parenting which have been largely ignored or unexplored.

Socioeconomic Status

Currently, only a small fraction of the world's population can control their fertility and approach ideal reproductive health. Adverse factors affect the majority of humans. These adverse factors are related to social, environmental, and cultural conditions in addition to the physical environment in which people live.

A consistent finding in almost all epidemiological studies of pregnancy outcome is that there is a major influence of socioeconomic status (SES), with a poorer prognosis being directly associated with lower levels of SES. The SES is a surrogate for influences which include: *a*) poor housing conditions, often in deprived areas, associated with poor hygiene, an inadequate supply of good quality water, a lower quality of indoor air, a higher level of exposure to pollutants, and infections; *b*) malnutrition; *c*) limited access to medical care; *d*) social drug use, in particular excessive alcohol consumption and smoking during pregnancy; *e*) the educational status of the mother.

Cultural Influences

In some regions of the world there are high levels of reproductive morbidity which are directly associated not only with SES, but also with cultural practices such as female circumcision. Women's health can be adversely affected when women cannot make decisions related to their well-being and reproductive aims. Men might seek large families as an economic resource and also as a demonstration of their virility, and women might then be expected to produce children. On the other hand, extramarital relationships and polygamy, low availability and not using contraceptives, high incidence of sexually transmitted diseases, and frequent illegal abortions in young women have been found to contribute to high infertility rates in certain cultures.

Vulnerability of Reproduction

Reproductive difficulties and developmental abnormalities constitute a significant medical problem and greatly contribute to human suffering. Every stage of reproduction is vulnerable to disruption by extraneous environmental agents causing problems with fertility, development, and maturation. This is related to social, cultural, economic, and physical conditions including nutrition and education. Adequate housing and hygienic conditions with safe water supplies are essential and reproductive health is particularly vulnerable to environments associated with poverty.

The reproductive process is particularly vulnerable to adverse environmental conditions including chemical pollutants and physical hazards such as irradiation. They have direct effects resulting in impaired fertility, high rates of abortions, and abnormal pregnancies as was dramatically demonstrated following the disaster which occurred at Chernobyl and Bhopal. Naturally occurring toxins such as high levels of arsenic in the water supply in parts of Mexico can reduce fertility in addition to causing other diseases.

The concentration of sperms in human semen has been reported to be declining over the past 50 years in apparently normal men. This observation may be related to the increasing levels of environmental pollution and may have significance for the future of male fertility.

Human exposure to environmental agents can affect the developing male and female germ cells causing impaired fertility. Exposure of the fertilized egg at the single cell stage, or in the very early stages of development when only a few cells are present, can produce either death of the structure or sublethal damage causing subsequent prenatal death, altered growth, structural abnormalities of the fetus, or postnatal death. At a later stage, when organs are developing, exposure may cause functional deficits or premature senescence.

Conception fails to achieve a normal pregnancy in the majority of cases. At least half of all fertilized eggs are eliminated naturally before or soon after they are embedded in the uterus. This is primarily associated with chromosomal abnormalities of the conceptus. Chromosomal abnormalities of various types have been found in 60% of all spontaneous abortions which occur in the first three months of pregnancy, associated predominantly with abnormalities in the number of chromosomes present. It is not known if the chromosomal changes are a response to environmental stimuli and refined methods of assessing the time interval between exposure and pregnancy are required. Population studies may help to discriminate between different exposure groups.

The process of implantation is poorly understood but may involve mechanisms similar to cancer biology and metastasis. Basic biological studies to discover the processes involved in implantation will have significant bearing on fertility management and may have important implications in other fields.

Intrauterine growth retardation (IUGR) is diagnosed when the developing fetus is smaller than expected for a

given period of gestation. Evaluation of the effects of fetal exposure to chemicals has concentrated mainly on congenital malformations and little attention has been given to alterations of normal fetal growth. However, IUGR should be considered as a toxicological end point in assessing the impact of the environment on reproduction, especially in those areas of the world where growth retardation is common and usually associated with infection, environmental hazards, and malnutrition. Some factors are known to be associated with IUGR such as cigarette smoking, consumption of drugs, and poor socioeconomic status. However, the exact cause remains unclear in most cases and the mechanisms involved are unknown. When environmental chemical insults cannot be clearly demonstrated, several different viral infections have been postulated. The development of good perinatal medical management has reduced mortality from respiratory, cardiovascular, and developmental diseases and has therefore increased the relative importance of IUGR as a cause of morbidity and mortality.

Developmental abnormalities of the fetus are recognized in 2–4% of all births. Although there is a genetic component associated with some human developmental anomalies, the cause of the vast majority of birth defects is not known. Approximately 20% of all live births are associated with some kind of genetic disorder but most of these do not produce recognizable developmental abnormalities. By school age, 12–14% of children show some behavioral or learning problems, or physical defects.

Organs develop not only during fetal life but also in the neonatal period and sometimes up to adolescence. Therefore, exposure to environmental agents at any time during fetal life can produce structural defects in developing organ systems such as the kidneys, the nervous system, and the skeleton. Exposure at these times may also cause cancer in the prenatal or postnatal periods, altered growth, functional deficits, perinatal death, or premature senescence.

Ideally, couples should have the opportunity to control their fertility and achieve their reproductive aims while maintaining their own health, the happiness of their sexual relationships, and the health of the offspring. It is estimated that at least 10–20% of couples suffer from the inability to achieve pregnancy; this figure is higher in many populations.

Environmental factors may have altered the duration of the reproductive period of life. In order to evaluate the influence of environmental exposure, the changes in ages of menarche and menopause can be used. Little is known about the affect of paternal exposure on pregnancy outcome and more investigation is required in this area, paying particular attention to hormone levels and their possible relation to reproductive health.

Breast Milk

Compounds in the maternal circulation can be excreted in breast milk, including environmental pollutants. In recent years, concern has been expressed about the health risks of infants exposed to environmental chemicals in breast milk, particularly PCBs, polychlorinated dibenzodioxins (PCDDs), and polychlorinated dibenzofurans (PCDFs). These chemicals are ubiquitous and have a long half-life in mammals. These compounds can be detected in human milk all over the world although their concentration is higher in inhabitants of industrialized countries. The manufacture and use of PCBs has been discontinued in many countries because of their toxicological properties and persistence. However, there are many sources of PCDDs and PCDFs, and their release into the environment is extremely difficult to control.

The nutritional, immunological, and psychological advantages of breast-feeding are well established, and the risk–benefit balance has been reevaluated in the light of recent data on the level of contamination of breast milk. Considering the current levels of contaminants in human milk and the relatively short time of exposure, it must be concluded that the proven advantages of breast-feeding far outweigh hypothetical health risks, and it should be unjustified to advise against breast-feeding. Nevertheless, every effort should be made to eliminate or substantially reduce the presence of these hazardous chemicals in the environment.

In some societies, women form the majority of the agricultural work force bringing them into contact with uncontrolled use of pesticides and other chemicals used in agriculture. This may adversely affect reproduction and increase contamination of breast milk.

Evaluation of the Impact of Environment on Reproductive Health

Animal Studies

Very low levels of chemicals can be detected in biological fluids enabling accurate and objective assessment of exposure. Recent advances in molecular biology have made it possible to examine specific genes which are susceptible to toxic substances. The technology is now available to improve assessment of the influence of the environment on human reproduction, but the implementation of such studies will require an increased allocation of resources to make use of existing knowledge and expertise and to continue with research in this important field.

In the future, animal models will continue to be a major tool for predicting human developmental hazards in view of the great difficulties involved in human assessments. The problem arises from the multifactorial etiology of developmental disorders, the comparatively low levels of environmental agents, and the extreme complexity of environmental exposures. The natural chemical background is also of importance. Both deficiency of essential elements and excess of natural chemicals can contribute significantly to the effect of man-made chemicals introduced into the environment.

While very detailed studies of reproductive and developmental effects of some environmental agents have been conducted with animals, information on humans is limited to a few well-documented agents such as lead, methyl mercury, DBCP, and PCBs.

Our ability to evaluate the impact of the environment on reproductive health has partly developed from animal testing procedures which were designed as a result of catastrophes causing reproductive and developmental abnormalities. For example, the thalidomide disaster focused attention on the need for screening pharmaceutical agents while the reproductive effects of lead and methyl mercury pointed out the need for testing environmental pollutants. Comparisons with human data indicate that animal models are generally predictive of the effects in humans.

Experience with the standard testing protocols used for reproductive and developmental evaluations suggests that they have served us well in preventing catastrophes. However, some improvements in testing protocols for more adequate assessment of reproductive effects are needed. In addition, incorporation of pharmacokinetic and pharmacodynamic information early in the process of evaluation could aid the selection of appropriate species and lead to the reduction in the number of animal studies.

In spite of the important role of animal studies in the prevention of reproduction failures, studies on humans are still needed and the social sciences have an essential part to play in filling the many gaps of knowledge which still remain. Unexpected combinations of exposure occur in humans and cultural or social effects are not reproducible in animal testing. Verification of experimental data must therefore involve epidemiological studies and information gained from the human experience.

Epidemiology

The influence of the environment on human reproduction is a concern in all countries and anxiety has been increased following disasters such as those which occurred at Chernobyl and Bhopal with their recorded and potential adverse effects. Accurate information about the reproductive consequences is required and this can be supplied by epidemiological studies when adequate data are collected.

Epidemiology is the basic science of public health and is the study of the determinants of disease. It can evaluate the magnitude of an effect and identify associated risk factors giving an insight into the development of prevention strategies. An essential prerequisite is the accurate and timely collection of relevant information in a systematic manner.

Current epidemiological methods use several controls which can simultaneously take into consideration many concomitant risk factors and exposure to different substances while assessing a variety of outcomes.

Surveillance is the dynamic, continual scrutiny of health-related events involving registration, tabulation, and analysis of health data. Surveillance of reproductive outcomes can provide the following: *a*) baseline rates of reproductive events, *b*) trends in reproductive health in geographic areas, *c*) an early indication of a risk factor affecting reproduction or development, and *d*) a system for monitoring the potential risk of acute events such as natural and human-generated disasters or the risk of newly introduced chemicals, including therapeutic drugs and chemicals used in agriculture and industry.

Role of Social Science

Promoting reproductive health is achieved by a harmonious interrelationship between humans and their environment. Assessing the reproductive health of a community should include cultural, ethnic, social, political, economic, and health factors. Developing strategies to achieve reproductive health should focus on solutions that are relevant to the reality of the community. These strategies should not be limited to protection of the community from the environment, but to develop a positive interaction between humans and their environment taking into consideration that the environment affects the person and the person affects the environment. This interaction is modulated by cultural, social, and political structures, and institutions at local, national, and international levels.

The nature and extent of adverse reproductive effects is related to both the socioeconomic conditions of the involved populations and to the exposure to the toxic agent(s). The SES may have different effects in different cultures and different geographical environments. The effect on reproductive health must be studied in relation to poverty and cultural factors such as use of contraceptives, sexual disorders, sexual habits, female circumcision and traditional beliefs. Cross-cultural studies must adopt conventional survey techniques to make them appropriate for the population under investigation.

Social scientists using quantitative methods to study large groups of humans can determine the socioeconomic structural patterns which influence reproductive behavior and reproductive outcomes. Qualitative studies of the behavior of smaller groups help the understanding of reproductive beliefs and motivations. Assessment of the quantitative and qualitative findings can give and insight into the risk factors which will predictably have an impact on reproductive health. In this way, the combined efforts of the scientific community will be instrumental in suggesting policies for the management of reproductive health programmes.

Reproductive health research by social scientists raises two major concerns. First, experience from developing countries shows that technological and economical developments have resulted in many adverse effects from which women and children suffer most. Yet, sociocultural impacts tend to be ignored by governments and policy makers in favor of economic growth. Second, in many industrialized countries attention has been focused on issues relating to the overuse of reproductive technology, the policy of intervention at parturition, and the approach to childbirth management which lacks informed consent. On the other hand, the accessibility, availability, and appropriateness of reproductive health care are major concerns in developing countries.

Strategies for Predicting and Preventing Adverse Reproductive Effects

Measuring the prevalence of disease in a population is essential for deciding priorities for tackling the major health problems at the local level. Epidemiology is required to put the problems in their proper perspective. Chemical pollution is known to have adverse effects on reproduction in industrialized countries, but infection and poor nutrition are more important factors in developing countries. There is a lack of quantitative comparative data to assess the relative effects of different factors on a worldwide perspective. Without this information, assessing the association between environmental factors and their total harmful effects on reproduction can only be speculative and prevention strategies can only be developed for regional rather than global populations. Even when there are factors which have proven effects on reproduction, verified with human data such as thalidomide, diethylstilbestrol and accutane, there is no real indication of either the scale of the effects or the relative risks of the different agents.

Epidemiological studies can complement animal data about the risk of environmental exposure to reproductive outcomes, but these studies must be designed to assess specific outcomes, the extent of the exposure, and the local availability of resources. As an example, surveillance of infant mortality in a community requires different resources and approaches as opposed to surveillance of congenital malformations. Surveillance systems of reproductive outcomes must be developed in response to the requirements of the local area and based on the priorities and needs of the community. In some areas, the priority might be surveillance of reproductive outcomes in an occupational health setting. The priority of another community may be surveillance of low birth weight. Planning surveillance should start with a review of existing data sources to determine if the required information is already available. The use of existing databases is generally desirable.

Discovering the crucial issues affecting human reproductive health will only be useful for improving the human condition worldwide if a reasonable strategy for tackling the problems is developed and implemented. Before implementing developmental programs, decisions must be based on an integrated assessment of the impact of the environment. Particular attention should be paid to the effect on vulnerable groups such as women and children, family units, and the entire community. Training and research in the social sciences will be required to assess the existing problems and the effect of intervention by appropriate corrective programs. An integrated database and surveillance study must be developed which will address specific issues of concern and will be multidisciplinary taking culture into consideration.

In spite of the large number of identified gaps in knowledge and research, it must be realized that information often already exists but is not known to the workers or is not used. Dissemination of information must be improved. A number of databases and registries at national and international levels have been created, but only a few have adopted the multidisciplinary integrated approach required and there is often duplication of effort and misuse of scarce resources. International standardization of systematic data collection and sharing of information has not been well-developed. A global strategy that is dedicated to health and eco-surveillance and is sensitive to national and regional problems must be formulated. The WHO can act as an international clearing house for these programs and such developments will be key elements for the prediction and prevention of adverse effects on reproductive health.

Health programs must have a worldwide basis with multidirectional international flow of information. The scientific community must assess the data and promote awareness of the problems at every level including the population and individuals affected in the local communities. Effective prevention of adverse health effects can only be achieved if scientific findings are reflected in a political commitment to implement necessary regulations.

Support Systems

One of the major obstacles to the effective implementation of sound environmental health policies is the lack of infrastructural support systems. Although such systems do exist in some countries, there is often fragmentation of responsibilities and infrastructural facilities are lacking in most developing countries. Some of the existing database and registry systems are listed in the appendix. The main categories of support system areas follow.

Reproductive Ecology Register. Reproductive ecology is the study of the causes and mechanisms of the effects of environmental risk factors on reproductive health and the methods of their prevention and management. A register could be prepared and maintained by the Human Reproduction Programme, WHO Geneva, and serve as an international resource for data retrieval and dissemination of information. It will need to establish interlinkages with other available and relevant databases and international organizations.

Environmental Protection Organizations. Organizations should be established to propose legislation and action related to protecting humans from the undesirable effects of environmental pollution and promoting relevant information being transmitted to the general public and organized interest groups. The biological, sociological, and demographic aspects of the environment must be protected. The Environmental Protection Agency (EPA) already exists in United States, and similar organizations are required in other countries.

Academic Faculties. Curricular reforms in education programs at the undergraduate, graduate, and postgraduate levels are required so that individuals educated in medicine, public health, nursing, engineering, social sciences, and law can respond sensitively to human needs in the context of environmental health.

Professional Associations. Postgraduate boards and colleges, professional scientific associations, and business

associations must promote awareness of possible risks of environmental pollution and knowledge about their prevention so that physicians, surgeons, obstetricians, gynecologists, geneticists, other health care personnel, industrialists, manufacturers, and organized labor groups can take appropriate action.

Nongovernmental Organizations (NGOs). NGOs contribute significantly to the work of national governments and international organizations such as WHO and the International Labour Organization (ILO). Through increased access to relevant information on environmental risk factors and their suspected impact on reproductive health, they can enhance communication with the public and promote close links between policy-making bodies at different levels.

It might be possible to identify environmental factors which have an impact on reproductive health and to describe conditions which would minimize the risk to human populations. This cannot be provided alone by medical personnel, health organizations, or scientists but can be affected by political will and commitment. A decision-maker must be made aware of the realities of the situation and their implications including resources needed for implementation. In a broader sense, responsible supportive communities could catalyze cultural changes.

Nutrition and Social Conditions

The effect of nutritional factors on reproductive health should be assessed with emphasis on insufficient or unbalanced food intake. A balanced diet with adequate protein and necessary nutrients is required. Specific dietary deficiencies or excesses of particular nutritional constituents and compounds are important and further investigation is required.

Deficiencies must be identified and corrected. Food should be derived from natural sources based on traditional diets in different cultures. Food and water should be continually monitored for contaminant or toxins and food production and distribution should be influenced by nutritional and medical requirements. Malnourishment must be counteracted, especially in pregnant women. It is important that attention should be paid in all countries not only to ensure an adequate supply of food but also to ensure that the quality of food in the shops is adequate. New methods of food production need to be monitored to ensure that hazards are not introduced.

Good family planning, prenatal, and perinatal medical care have a clear beneficial effect on the outcome of pregnancy. Availability and participation in vaccination programs have had a major influence on child health. Adequate provision of resources to improve housing conditions and install better water supplies and sewage facilities could greatly improve the reproductive health of women.

Workplace and Industrial Pollution

Access to fresh air, clean water, and safe sanitation should be available, and the condition of the workplace should not be harmful to the reproductive capacity or function of males or females.

Worker migration often leads to disruption of the family unit and can be associated with an increased incidence of sexually transmitted diseases. Working conditions must take into consideration the double role of reproducing women in employment ensuring that there are no adverse effect on them or their offspring. This will involve paid pregnancy and maternity leave before and after delivery and appropriate arrangements for breast-feeding.

Exposure to industrial pollution in the workplace and elsewhere in general must be controlled using modern technology and working practices. New chemicals must be continually assessed to determine exposure levels and possible impact on reproductive health. This monitoring should also apply to physical factors such as noise and microwaves. Medical and research personnel should be aware of reproductive health dangers and should implement protective measures.

Education and Improvement of Women's Status

A universal and appropriate education regardless of gender or social status will improve the status of women and their families, and increase individual freedom of choice. Better education of women would lead to increased awareness of the importance of good medical care and the risks associated with excessive use of social drugs. It should lead to improvement in the social status and general attitudes towards women, improving their status and role in society. Education includes information about life style which may be related to spontaneous abortion, developmental abnormalities, and other adverse effects of reproductive outcome. Women should be given equal opportunities at work, in the use of health services, and in society at large. Better education and improved status of women would have the greatest impact on the prevention of reproductive hazards and is a strong factor in the control of family size.

Contraception and Sexual Behavior

Sex education should be included in general education and specific instruction about the diversity of contraceptive methods and sexually transmitted diseases is essential. Ideally, every woman should have access to medical assistance in their choice and control of contraceptive use in order to prevent unwanted pregnancies. All contraceptives should be continually assessed for undesirable side effects.

Induced termination of pregnancy is at serious risk of complication if performed illegally and in unsafe conditions. All women should have access to authorized termination performed by medical personnel.

Action should be taken to protect women in particular, but also children and men, from any kind of sexual assault or violence, and provision for the safety of women and vulnerable people should be available.

Disaster Team and Watch Dog Organizations

The possible health hazards of unexpected disasters such as the Chernobyl explosion or the Middle East war should result in immediate action being taken by international organizations including the UN, WHO, and EEC. Their expertise and resources should be mobilized with access to special reserve funds and reproductive health hazards should be one of their main concerns. The dose of chemicals or radiation released into the environment must be calculated and the exposure dose assessed.

The international level of environmental and occupational factors which affect reproductive health should be evaluated continually or intermittently by groups of experts. This could be performed by an international organization similar to IARC which could be established under the auspices of WHO in collaboration with labor organizations and governmental authorities in different countries. This organization would issue proper guidelines for hazard assessment and would supply information to developing countries. They could establish standardized protocols for assessing reproductive failures and provide training and education of personnel for this type of work. Such an international network would be dependent on expertise in all countries and could result in international integration of existing surveillance and assessment.

Research Priorities and Unmet Research Needs

The methodology currently available can answer many questions about the risk of environmental agents to human reproduction. The research needs that have not been met are largely a consequence of limited financial resources and personnel. Priority should be given to studies that combine international collaboration with standardized objectives and methods where information is required about existing exposures in developing countries. Developed countries require improved dose–response assessment with evaluation of uncertainties and understanding the mechanisms involved in the outcomes produced.

Animal studies can suggest possible adverse reproductive effects of substances, but the real effects can only be assessed in human populations which are presently exposed to these substances. The influence of cultural, dietary, genetic, and socioeconomic differences will confound the results of human surveys and further studies will be required to examine the importance of the different factors.

The detection and surveillance of environmental exposures depends on valid laboratory data in addition to quality assurance and quality control of laboratory test procedures. The priorities of future research needs are: *a*) promoting social and gender equality with community participation in order to improve reproductive health and outcomes, *b*) developing multidisciplinary studies that are analytical, problem solving, and action oriented, and will have policy implications, and *c*) promotion of local, national, and international cooperation in future research.

Future research must promote health while optimizing the use of available resources. Attention must be paid to the interdependence and interaction of humans and the environment. Cost containment has created particular difficulties in decision-making and a balance must be struck assessing the relative values of human needs and developing technological advances.

Unmet Research Needs in Basic Biology

An understanding of the basic mechanisms underlying human reproduction is essential because advances in medical care evolved from basic research findings. The physiology of human reproduction and the importance of the neuroendocrine system have been well studied, but there is still much to learn about cell and molecular biology to elucidate the key genes involved in reproduction which are the most likely targets for alteration by environmental factors. Gene probes should be developed to provide a basis for molecular epidemiology (important for cancer prevention strategies) and could be developed to elucidate the genetic risk factors for environmentally induced reproductive dysfunction.

Many environmental agents require metabolic activation in order to produce their biological effects. Some genes produce certain forms of enzymes that are associated with an increased risk of developing cancer, but the role of such genes in reproductive health has not been investigated in humans. Some inbred species of mice are known to have a highly inducible enzyme and have also been observed to be at increased risk of developing malformation. The genetic basis of this should be examined.

Reproductive health is affected by stress but the exact mechanisms are unclear. Stress at the cellular level in response to internal or external stimuli produces a variety of isochemical responses. The stress effect at the molecular and cellular levels in cells and tissues is important in reproduction and should be examined to assess the internal counterpart of interpersonal effects.

Biomarkers are reproducible biochemical or molecular changes which can be detected as a result of exposure to environmental factors and can be indicators of both exposure and effect. Research of cancer biomarkers is much more advanced than biomarkers of reproductive dysfunction and support in this field could provide important clinical tests of exposure and effect.

Environmental agents can affect DNA but the association between damaged DNA in the sperm and reduction in male fertility is unclear. Environmentally induced mutations may have either direct effects on reproductive tissue or may affect the germ cells and be passed onto successive generations. Such specific mutations which are relevant to reproduction must be investigated. For example, genetic polymorphisms in the estrogen receptor are associated with a higher prevalence of spontaneous abortion. Experience with cancer studies suggests that useful information can be derived from similar investigations of reproductive dysfunction.

Conflicting reports are produced because of inconsistency of available results. This is due to lack of standardiz-

ation of the design of studies and greater harmonization of protocols will give a more accurate assessment of the effect of chemical, physical and biological agents. The effect of chemicals with hormone like activity and their interference with reproduction must be elucidated. More systematic assessments of the effects of pollution on water, soil, food, and air are needed.

The aim of more refined and standardized assessment methods is to lower the contamination of the environment and reduce exposure to potentially hazardous substances. In this regard, the creation of a multidisciplinary multinational research group will help to minimize the adverse effects on human fertility, paying particular attention to pesticide exposure which may be the most significant environmental pollutant. Such a group could respond to international disasters which have potentially catastrophic effects on human reproduction.

Recommendations

To address the concerns about the impact of the environment on reproductive health, there is a need to generate more public awareness and political will. To guide the process of informed decision-making, the following recommendations are proposed: 1) promote international research collaboration, emphasizing *a*) international harmonization of methodological approaches for assessing developmental and reproductive toxicity; *b*) development of reproductive ecology surveillance mechanisms and international databases; *c*) strengthening of international disaster alert and evaluation systems; and *d*) establishment and strengthening of research linkages between scientists in developed and developing countries. *2*) Promote research capabilities, emphasizing *a*) development of problem-solving multidisciplinary studies that are analytical and action oriented and which have policy implications; *b*) interaction of environmental factors with cellular processes and basic studies to develop better markers of the effect of exposure on reproductive functions; and *c*) expansion of training and education in the required disciplines for research into reproductive health. 3) Tackle the priority problems identified, which include *a*) exposure to chemical, physical and biological agents as well as stress at the workplace and at home in relation to human fertility and reproductive health; *b*) exposure of different populations to pesticides; and *c*) inadequate screening methods for identification of many thousands of environmental chemicals which require further detailed investigation.

Appendix

List of Existing Databases and Registries

- Developmental and Reproductive Toxicology Database (DART) (continuation of ETIC). Bibliographic database on the TOXNET system of the National Library of Medicine
- International Clearinghouse for Birth Defects Monitoring Systems (ICBDMS). (E. Castilla, Chairman)
- International Register of Potentially Toxic Chemicals (IRPTC/UNEP). Interactive actual database including all toxicity and ecotoxicity end points as well as hazard evaluations. (Palais des Nations, Geneva, Switzerland)
- Chemical Information System (CIS/ILO). Bibliographic database including occupational exposure data and health risks
- European Registration of Congenital Anomalies (EUROCAT). (Ecole de Sante Publique UCL, Brussels, Belgium)
- Reproductive Toxicology Center On-line Reviewed Database. (Columbia Hospital for Women, Washington DC)
- Interative Database (A. Scialli, Director)
- Teratology Information Service. International network of systems (J. O'Brien, Boston)

The views expressed in this paper reflect the opinions advanced by all the participants and are not necessarily the views of the editor nor of the World Health Organization or other institutions that collaborated in the organization and support of the workshop. This summary is not a policy statement of the workshop.